

IN THE SPECIFICATION

Amend the specification as follows:

Page 1, delete the paragraph starting on line 1 after the title which was added by way of the Amendment dated July 6, 2001, and insert the following therefor:

This application is a divisional of Application No. 08/362,455, filed January 11, 1995, which is a 371 U.S. national phase of PCT/EP94/01323, filed April 27, 1994, which designated the U.S., the entire content of which is hereby incorporated by reference in this application.

Page 33, delete the paragraph spanning lines 28-33 and insert the following therefor:

- M44, Q70, A87, N106, K115, V137, G142, P165, I178, F251, A299, N303, Q317 which are specific for the Core/E1 region of the HCV ~~type 4 sequence~~ type 5 sequence of the present invention as shown in Fig. 5;

Page 39, delete the paragraphs spanning lines 11-33 and insert the following therefor:

- a sequence having a homology of more than 80%, preferably more than 82%, most preferably more than 84% homology to any of the amino acid sequences as represented in SEQ ID NO ~~118, 120, and 122~~ 119, 121, and 123 (GB358, GB549,

GB809 sequences) in the region spanning positions 127 to 319 of the Core/E1 region as shown in Figure 5;

- a sequence having a homology of more than 73%, preferably more than 75%, most preferably more than 78% homology in the E1 region spanning positions 192 to 319 to any of the amino acid sequences as represented in SEQ ID NO ~~118, 120, and 122~~119, 121, and 123 (GB358, GB549, GB809 sequences) in the region spanning positions 140 to 319 of the Core/E1 region as shown in Figure 5;

- a sequence having more than 85%, preferably more than 86%, most preferably more than 87% homology to any of the amino acid sequences as represented in SEQ ID NO ~~118, 120 or 122~~119, 121, or 123 (GB358, GB549, GB809 sequences) in the region spanning positions 192 to 319 of E1 as shown in Figure 5;

- a sequence showing more than 73%, preferably more than 74%, most preferably more than 75% homology to any of the amino acid sequences as represented in SEQ ID NO ~~106, 108, 110, 112, 114 or 116~~107, 109, 111, 113, 115 or 117 (GB48, GB116, GB215, GB358, GB549, GB809 sequences) in the region spanning positions 2645 to 2757 of the NS5B region as shown in Figure 2;

- a sequence having any of the sequences as represented in SEQ ID NO 164 or 166 (GB809 and CAM600 sequences) in the Core-E1 region as shown in Figure 5;

- a sequence having any of the sequences as represented in SEQ ID NO 168, 170, 172, 174, 176, 178, 180, 182, 184, 186, 188 or 190 (CAM600, GB809, CAMG22, CAMG27, GB549, GB438, CAR4/1205, CAR4/901, GB116, GB215, GB958, GB809-4 sequences) in the Core/E1 region as shown in Figure 5;

Page 40, delete the paragraph spanning lines 1-3 and insert the following therefor:

- a sequence having any of the sequences as represented in SEQ ID NO 192, 194, 196, ~~198, 200~~, 202, 204, 206, 208, 210, 212 (GB358, GB724, BE100, PC, CAM600, CAMG22, etc.) in the NS5B region or in SEQ ID NOs: 198, 200 in the NS3/4 region.

Page 40, delete the paragraph spanning lines 22-25 and insert the following therefor:

- a sequence having more than 90%, preferably more than 91%, most preferably more than 92% homology to any of the amino acid sequences represented in SEQ ID NO 56 ~~to~~ 58 (PC sequences) in the region spanning positions 1286 to 1403 of the NS3 region as shown in Figure 7 or 11;

Page 46, delete the paragraph on line 1 and insert the following new paragraph therefor:

Figure Legends Brief Description of the Drawings

Page 51, delete the paragraphs spanning lines 3-25 and insert the following therefor:

In total, 8 clones covering the core/E1 region of 3 different isolates were sequenced and the E1 portion was compared with the known genotypes (Table 3) as

shown in Figure 5. After computer analysis of the deduced amino acid sequence, a signal-anchor sequence at the core carboxy terminus was detected which might, through analogy with type 1b (Hijikata et al., 1991), promote cleavage before the LEWRN sequence (position 192, Fig. 5; SEQ ID NO:271). The L-to-P mutation in one of the HD10-2 clones resides in this signal-anchor region and potentially impairs recognition by signal peptidase (computer prediction). Since no examples of such substitutions were found at this position in previously described sequences, this mutation might have resulted from reverse transcriptase or *Pfu* polymerase misincorporation. The 4 amino-terminal potential N-linked glycosylation sites, which are also present in HCV types 1a and 2, remain conserved in type 3. The N-glycosylation site in type 1b (aa 250, Kato et al., 1990) remains a unique feature of this subtype. All E1 cysteines, and the putative transmembrane region (aa 264 to 293, computer prediction) containing the aspartic acid at position 279, are conserved in all three HCV types. The following hypervariable regions can be delineated: V1 from aa 192 to 203 (numbering according to Kato et al., 1990), V2 (213- 223), V3 (230-242), V4 (248-257), and V5 (294-303). Such hydrophilic regions are thought to be exposed to the host defense mechanisms. This variability might therefore have been induced by the host's immune response. Additional putative N-linked glycosylation sites in the V4 region in all type 1b isolates known today and in the V5 region of HC-J8 (type 2b) possibly further contribute to modulation of the immune response. Therefore, analysis of this region, in the present invention, for type 3 and 4 sequences has been instrumental in the delineation of epitopes that reside in the V-regions of E1, which will be critical for future vaccine and diagnostics development.

Page 51, delete the paragraphs spanning lines 27-30 and insert the following therefor:

For the NS3/NS4 border region, the following sets of primers were selected in the regions of little sequence variability after aligning the sequences of HCV-1 (Choo et al., 1991), HCV-J (Kato et al., 1990), HC-J6 (Okamoto et al., 1991), and HC-J8 (Okamoto et al., 1992) (smaller case lettering is used for nucleotides added for cloning purposes):

Delete the paragraph spanning page 60, line 26 to page 61, line 2 and insert the following new paragraph therefor:

Primers HCP_r52(+): 5'-atgTTGGGTAAGGTCATCGATACCCT-3' (SEQ ID NO:80), HCP_r23(+): 5'-CTCATGGGGTACATTCCGCT-3' (SEQ ID NO:67), and HCP_r54(-): 5'-CTATTACCAGTTCATCATCATATCCCA-3' (SEQ ID NO:68), were synthesized on a 392 DNA/RNA synthesizer (Applied Biosystems). The sets of primers HCP_r23/54 and HCP_r52/54 were used, but only with the primer set HCP_r52/54, PCR fragments could be obtained. This set of primers amplified the sequence from nucleotide 379 to 957 encoding amino acids 127 to 319: 65 amino acids from the carboxyterminus of core and 128 amino acids of E1. The amplification products GB358-4, GB549-4, and GB804-4

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were cloned as described in example 1. The following were obtained from PCR fragments:

Page 70, delete the contents of page 70 and insert the following therefor:

Table 6. NS4 sequences of the different genotypes

| prototype | TYPE | SYNTHETIC PEPTIDE NS4-1 (NS4a) | SYNTHETIC PEPTIDE NS4-5 (NS4b) | SYNTHETIC PEPTIDE NS4-7 (NS4b) |
|------------|------|---|---|--|
| position-> | | 1 6 9 0 | 1 7 2 0 | 1 7 3 0 |
| HCV-1 | 1a | *** ** ** LSG KPAIIPDREV LYREFDE (SEQ ID NO:272) | * * * SQHLPYIEQ GMM L AEQFKQ K (SEQ ID NO:273) | * * * * L AEQFKQ K A LGLLQTAS RQA (SEQ ID NO:274) |
| HCV-J | 1b | LSG RPAVIPDREV LYQEFDE (SEQ ID NO:275) | ASHLPYIEQ GMQLAEQFKQ K (SEQ ID NO:276) | L AEQFKQ K A LGLLQTAT KQA (SEQ ID NO:277) |
| HC-J6 | 2a | VNQ RAVVAPDKEV LYEAFDE (SEQ ID NO:278) | ASRAALIEE GQRIAEMLKS K (SEQ ID NO:279) | IAEMLKS KIQGLLQOAS KQA (SEQ ID NO:280) |
| HC-J8 | 2b | LND RVVVPDKEI LYEAFDE (SEQ ID NO:281) | ASKAALIEE GQRM A EMLKS K (SEQ ID NO:282) | M AEM L KS KIQGLLQOAT RQA (SEQ ID NO:283) |
| BR36 | 3a | LGG KPAIIVPDKEV LYQQYDE (SEQ ID NO:97) | SQAAPYIEQ AQVIAHQFKE K (SEQ ID NO:99) | IAHQFKE KVLGLLQ R AT Q Q Q (SEQ ID NO:100) |
| PC | 5 | LSG KPAIIPDREA LYQQFDE (SEQ ID NO:102 and SEQ ID NO:103, respectively) V | AASLPYMD E TRAIAGQFKE K (SEQ ID NO:284) | IAGQFKE KVLGFISTTG Q KA (SEQ ID NO:105) |

*, residues conserved in every genotype. Double underlined Underlined amino acids are type-specific, amino acids in italics are unique to type 3 and 5 sequences.

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Insert the attached Sequence Listing in place of the Sequence Listing filed with
July 6, 2001.